Clinical Practice Guidelines for Diagnosis and Management of Hypersensitivity Reactions to Quinolones

Brief running title: Diagnosis and Management of Hypersensitivity to Quinolones

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0669

Abstract

Over recent years, the consumption of quinolones as first-line treatment has increased, leading to a growth in incidence of hypersensitivity reactions (HSRs) to this group of antibiotics. Both diagnosis and management of HSRs to quinolones are complex and controversial. These practical guidelines aim to provide recommendations for an effective clinical practice. With this purpose, an expert panel reviewed the literature regarding HSRs to quinolones and analyzed controversies in this area.

Most HSRs to these drugs are immediate and severe, being the risk for HSR higher in subjects who reported allergy to betalactams, moxifloxacin-induced anaphylaxis and immediate reactions (IRs) compared with patients who reported reactions to quinolones inducing other symptoms. Regarding diagnosis of HSRs to quinolones, the usefulness of skin tests is controversial, with sensitivity and specificity varying among studies. Most *in vitro* tests are produced in-house, with no validated commercial ones and basophil activation test being useful for diagnosing IRs although with diverse results regarding sensitivity. Drug provocation test is nowadays the gold standard for confirming or excluding the diagnosis as well as to find safe alternatives, although contraindicated for severe reactions. Cross-reactivity among quinolones is controversial among different studies, with the lowest cross-reactivity for levofloxacin. Desensitization may be considered in allergy to quinolones when no other alternative exist.

Key words: Drug allergy. Quinolones. Anaphylaxis. Skin test. Drug provocation test. Basophil activation test.

Resumen

En los últimos años ha aumentado el consumo de quinolonas como tratamiento de primera línea, lo que ha dado lugar a un aumento de la incidencia de reacciones de hipersensibilidad (RHS) a este grupo de antibióticos. Tanto el diagnóstico como el manejo de las RHS a las quinolonas son complejos y controvertidos. Esta guía tiene como objetivo ofrecer recomendaciones para una práctica clínica eficaz. Con este propósito, un panel de expertos ha revisado la literatura sobre las RHS a quinolonas y ha analizado las controversias en esta área.

La mayoría de los RHS a estos fármacos son inmediatas y graves, siendo el riesgo de sufrir una RHS más alto en los sujetos que reportaron alergia a betalactámicos, anafilaxia inducida por moxifloxacino y reacciones inmediatas en comparación con otras quinolonas y otros síntomas. En lo que respecta al diagnóstico de las RHS a quinolonas, la utilidad de las pruebas cutáneas

es controvertida, ya que la sensibilidad y la especificidad varían de un estudio a otro. La mayoría de las pruebas *in vitro* se producen en cada centro, sin que existan pruebas comerciales validadas, y aunque la prueba de activación de basófilos es útil para el diagnóstico de las IRs, los resultados obtenidos son diversos en cuanto a sensibilidad. La prueba de provocación es hoy en día el patrón de oro para confirmar o excluir el diagnóstico, así como para encontrar alternativas seguras. Existen controversias con respecto a la reactividad cruzada entre las quinolonas en los diferentes estudios, siendo el levofloxacino la que induce menor reactividad cruzada. En los pacientes con diagnóstico de RHS confirmada a quinolonas, se puede considerar la desensibilización cuando no existe ninguna otra alternativa.

Palabras clave: Alergia a medicamentos. Quinolonas. Anafilaxia. Tests cutáneos. Test de provocación. Test de activación de basófilos.

Prologue

The objective of these guidelines is to provide useful information to ensure efficient and effective clinical practice in the diagnosis and management of hypersensitivity reactions (HSRs) to quinolones. They were developed by a group of expert allergy specialists from the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (SEAIC) with considerable experience in the evaluation and management of drug-induced HSRs and extensive experience in research. A bibliographic search on studies regarding HSRs to quinolones was performed including the available scientific evidence up to September 2020. The main sources for the search included electronic databases (MEDLINE and PubMed), electronic libraries (Science Direct, OVID), and a systematic review database (Cochrane Library). We considered the articles regarding prevalence, pathogenesis, clinical manifestations, diagnosis, and treatment of HSRs to quinolones. The key words used were quinolone, the name of each quinolone (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, lomefloxacin, gatifloxacin, oxolinic acid, nalidixic acid, and pipemidic acid), as well as the terms allergy, hypersensitivity, anaphylaxis, immediate reactions (IRs), non-immediate reactions (NIRs), delayed reactions, skin test (ST), skin prick test (SPT), intradermal test (IDT), *in vitro* test, drug provocation test (DPT), and desensitization. From the articles found, we selected only original articles or systematic reviews. We excluded non-systematic reviews, comments and other types of studies. Grades of recommendation were discussed by the whole group and defined according to the Scottish Intercollegiate Guidelines Network [1]. Wherever evidence was lacking, a consensus among the experts was reached.

Introduction

The clinical usefulness of quinolones is increasingly extensive taking into account its wide range of antibacterial activity and easy administration. Several epidemiological studies show that, over recent years, the consumption of this group of antibiotics as first-line treatment has raised [2-4].

Quinolones are generally well-tolerated; however, HSRs and phototoxicity to these drugs have been reported. Indeed, the incidence of HSRs involving quinolones has multiplied by 10 in recent years [5-7], currently representing one of the most frequent causes of consultations for suspected allergic reactions to medications [6, 8]. It has become an important health problem as in 70% of cases HSRs can be severe, including anaphylactic reactions and toxic epidermal necrolysis (TEN) [2, 9-12]. According to some studies, quinolone-induced anaphylaxis represents 4.5% of drug-induced anaphylaxis [13].

The diagnostic procedure can represent a challenge as clinical history is often unreliable and STs and *in vitro* tests have important limitations [2]. Therefore, DPT is considered the gold standard to establish diagnosis, which is not a risk-free procedure [2, 14].

In addition, HSRs to quinolones have also been associated with beta-lactam agent allergies, reducing the safe alternative for these patients [15].

Therefore, the scenario we are facing is very complex and it is essential for the allergist to become familiar with the peculiarities of diagnosis and treatment of HSRs to this group of antibiotics.

Classification, chemical structure, and mechanism of action

Quinolones form drug-enzyme-DNA complexes, in which the DNA is broken, by direct inhibition of two bacterial enzymes: DNA gyrase and topoisomerase IV [16, 17]. They have a fast bactericidal and dose-dependent activity. Structurally, quinolones are composed of the 4-oxo-1,4-dihydroquinoleine ring core with a nitrogen atom at position 1, a carbonyl at position 4, and a carboxyl at position 3. Since the beginning of its synthetization [18], several structural changes have been introduced, improving antimicrobial effectiveness and the broadening of the antibacterial spectrum of quinolones, with better bioavailability, greater tissue penetration and, consequently, long half-life [19]. Therefore, quinolones have been classified into four different groups, based on their chemical structure and their antibacterial spectra [19-21] (Figure 1). The **first generation quinolones** (oxolinic acic, nalidixic acid, cinoxacin, and pipemidic acid) have activity against enterobacteria and some Gram-negative. They are mainly administered by oral route, reaching low systemic levels and high concentrations in urine, being commonly used urine antiseptics. The introduction of the fluorine atom at position C-6 led to the development of the group of fluoroquinolones (**Second generation quinolones:** ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, fleroxacin, lomefloxacin, enoxacin**)** with broad spectrum potent antibacterial activity, including against Gram-negative, and an alkylated pyrrolidine or piperazine at C7, which increases serum half-life and potency against Gram-positive bacteria. A halogen (F or Cl) at the 8-position (**Third generation quinolones:** levofloxacin and gatifloxacin) improves oral absorption and activity against *P. aeruginosa*, Gram-positive, and anaerobes [22]. Finally, **the fourth group** (moxifloxacin, gemifloxacin andtrovafloxacin) has better activity against Gram-positive and anaerobes due to a double ring derived from the pyrrolidonic ring in 7-position and a methoxy group in 8-position, although it decreases its activity against *P. aeruginosa*.

Pathogenesis of HSRs to quinolones

HSRs to quinolones can be classified into IRs or NIRs, depending on the time interval between the drug intake and the onset of the reaction [2, 23]. Typically, IRs occur within the first hour following the first administration of a new course of treatment, although pathophysiologically it can be considered a time interval up to 6 hours after the quinolone administration [23]. NIRs may occur any time as from 1 h after the initial drug administration, commonly occurring after many days of treatment [23].

The most frequently described reactions are IRs [2, 10, 12, 15, 24], which include urticaria, angioedema, and anaphylaxis, suggesting an IgE-mediated response resulted from mast cell and/or basophil degranulation triggered by cross-linking of IgE/FcERI. Indeed, IgE antibodies to ciprofloxacin and other quinolones in serum have been detected in the 30-55% of patients with confirmed allergic IRs to these drugs, which have demonstrated high specificity to quinolones as has been confirmed by inhibition assays [9, 25]. It is important to take into account that a HSR may occur in the absence of previous exposure to quinolones if patient is presensitized by exposure to apparently unrelated chemical compounds, as has been reported for neuromuscular blocking agents (NMBAs) [26]. Specific IgE against quaternary ammonium has been determined in 53% of patients with confirmed IRs to quinolones [27], therefore it could be hypothesized that this component may be involved in the origin of IgE quinolone HSR in naïve patients. However, this fact has not been confirmed and the *in vivo* relevance of these findings remains unclear.

Nevertheless, not all IRs are mediated by drug-specific IgE (sIgE), although the clinical symptoms are indistinguishable from those IgE-mediated. Actually, an increasing number of studies have demonstrated and/or speculated on the ability of quinolones and others drugs to trigger mast cell activation and degranulation via occupation of the Mast-related G-protein receptor X2 (MRGPRX2) [28-35]. In experimental models in vivo and in vitro studies demonstrated the capacity of fluoroquinolones for activating mast cells and inducing mediators release in wild type being reduced in MrgprB2^{MUT} mice [28]. Moreover, this activation by ciprofloxacin can be inhibited by an antagonist of MRGPRX2, the tripeptide QWF (glutaminyl-D-tryptophylphenylalanine), as also demonstrated in in vitro and animal models [29, 36]. This off-target alternative mechanism of mast cell activation may explain positive STs seen in healthy control individuals [22, 37], potentially reflecting the potent non-specific mediator release [38-40].

Recently, it has been reported that MRGPRX2 is not exclusively expressed on mast cells, but also on basophils and eosinophils, and that ciprofloxacin might mediate its effect by enhancing

MRGPRX2 surface expression on basophils and eosinophils and inducing degranulation by binding to this receptor [41]. In this case the evaluation of these reactions using BAT can produce false positive results. However, others indicate that basophils barely express MRGPRX2, and HSR from MRGPRX2 occupancy will probably yield negative BAT results [33].

Anyway, whatever the situation, unlike IgE-dependent reactions, BAT seems not to be the best tool for evaluating MRGPRX2 mediated reactions [35, 42]. Addittionally, cases with positive responses in both STs and BAT are more prompted to be IgE/FcεRI-dependent reactions [9, 15, 29, 32, 43-48].

It is of note that despite the involvement of this receptor in fluoroquinolone-induced mast cell activation, the fact that this receptor is present in everybody but only minority of subjects experience HSR to this drug class indicates that other factors must be involved in predisposed subjects. This predisposition to immediate drug-induced reactions may be related to single nucleotide polymorphisms resulting in a hyperactivation by changing the structure of the receptor MRGPRX2 and receptor binding sites [35], epigenetic modifications due to environmental influences [35], post-transcriptional modifications resulting in synthesis of MRGPRX2 variants, temporarily or constitutively varying surface expressions and even the influence of co-factors [35].

Despite the mechanism involved in mast cell/basophil degranulation, the steps for diagnosing and managing patients that suffer a reaction after quinolones intake are similar, although we must be aware of false positive ST results and false negative BAT results that may be produced by MRGPRX2 mediated activation.

NIRs are thought to be T cell-mediated. However, the immunogenicity of quinolones for T cells has not been studied in detail yet [49-51]. Two models describe how quinolones, as small molecular compounds ($\leqslant$ 1000 Da), might interact with immune proteins to elicit T cell reactivity: i) the hapten model postulates that the drug binds covalently to a macromolecular carrier, such as a larger endogenous peptide or protein, to generate neoantigen that stimulates a T cell response [52, 53]; ii) the P-I model proposes that a small molecule can bind to HLA in a non-covalently way to directly stimulate T cells [48, 54, 55]. This results in the presentation of novel peptide ligands that may elicit an immune response.

IRs and NIRs to quinolones can be induced by the relevant quinolone without the necessity of metabolism or processing. However, the possibility that quinolone metabolites could induce a HSR cannot be excluded, although to our knowledge no published evidence exists.

Epidemiology and risk factors

Although HSRs to quinolones are considered unusual, their incidence is increasing [10, 56, 57], due in part to the raise in their prescription [4, 5] and the introduction of potentially more immunogenic quinolones such as moxifloxacin [12, 15, 24, 57, 58]. Particularly, in Spain, it increased from 0.53% in 2005 to 5.96% in 2009 [6]. In the case of children, the estimated risk of suspected adverse reactions to quinolones has been reported as 0.046% [45]. They have positioned as the third cause of confirmed HSRs to drugs, being the group of non-beta-lactam antibiotics most frequently involved in HSRs [6]. Among hospitalized patients, quinolones are the second group of antibiotics referred in drug alerts or intolerances [59].

Based on spontaneous reports of quinolone-induced anaphylaxis, an incidence of 1.8-2.3 cases per 10,000,000 days of treatment is estimated, representing the 4.5% of anaphylaxis caused by drugs [13]. In fact, the risk for developing HSRs may be different among quinolones and has been reported to be 96 times higher in subjects who reported moxifloxacin-induced anaphylaxis, and 18 times higher in those reporting IRs, compared to subjects who experience clinical entities induced by quinolones other than moxifloxacin and NIRs [12]. The risk for suffering an IR to quinolones is up to 4 times greater when moxifloxacin is the culprit, compared with other quinolones [12, 60]; ciprofloxacin has been associated with a 6-fold increased risk of having a severe delayed skin reaction [60]; and norfloxacin, ofloxacin, and ciprofloxacin with an increased risk of acute generalized exanthematous pustulosis (AGEP) [2, 60, 61]. In addition, quinolones in general have been associated with high risk of Stevens-Johnson syndrome (SJS) and TEN [62]. Old age, concomitant levothyroxine treatment, and HIV infection have been described as factors associated with poorer prognosis in SJS and TEN [60]. Moreover, HIV-infected adult patients also have more frequently reactions to ciprofloxacin, including anaphylaxis [56]. There is also a risk of hepatotoxicity by quinolones especially in patients with alcohol intake [63].

It has been published that 21% of patients allergic to beta-lactams develop allergy to other antibiotics such as quinolones, compared with 1% who are not allergic to beta-lactams [64]. It has been estimated that having an IR to beta-lactams increases 23 times the risk of having a HSR to quinolones [15] (level of evidence 2+). It is not clear whether there is an individual predisposition to have HSRs to drugs or whether due to previous allergy to beta-lactams patients are more likely to be prescribed a quinolone, therefore more studies are needed to clarify the mechanisms involved in this association. Due to quinolones may induce mast cell degranulation mediated by MRGPRX2 patients with mastocytosis have an increased risk of HSR of up to 50% [34].

Clinical symptoms

IRs to quinolones are the most common type of HSRs to these drugs [2, 10, 12, 15, 24, 57]. They are characterized mainly by the presence of urticaria/angioedema (31.6-85%), anaphylaxis (32.8-62.5% of cases), and anaphylactic shock (13-26.3%) [9, 12, 25, 37, 46, 58] (Table 1) (level of evidence 2+). Although all quinolones can induce IRs, the rate of reactions by moxifloxacin is higher than with other quinolones, specifically in anaphylactic reactions [10, 12, 15, 24, 58]. Indeed, 70% of reactions induced by moxifloxacin are anaphylaxis [12] (level of evidence 2+). Cases of Kounis syndrome induced by ciprofloxacin [65], cinoxacin [66], and levofloxacin [67] have been also reported (level of evidence 3).

NIRs to quinolones are less frequent than IRs [2, 12]. Delayed urticaria and maculopapular exanthemas (MPE) are the most common NIRs, being usually not severe [12, 15, 37, 68, 69] (Table 1) (level of evidence 2+). Ciprofloxacin has been reported as the main responsible [12], although other quinolones can be involved [12, 15, 68-70] (level of evidence 2+). Another common type of NIR is fixed drug eruption (FDE) [12, 68], which has been reported with ciprofloxacin [12, 71], norfloxacin [12, 72], levofloxacin [73], moxifloxacin [12], and gemifloxacin [37], with the possibility of cross-reactivity among them described [71-74] (level of evidence 3). Cases of drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) and AGEP induced by different quinolones have been published [61, 68, 69, 75] (level of evidence 3). In addition, less frequent entities such as SJS and TEN have been reported [76], being quinolones described as a causative agent in 8.48% of this type of reactions [76] (level of evidence 3). Regarding SJS/TEN [77-80], ciprofloxacin has been reported as the most frequent quinolone involved, although cases have also been associated with other quinolones as levofloxacin [81, 82], ofloxacin [83], moxifloxacin [84], and trovafloxacin [85] (level of evidence 3).

Quinolones are among the most frequent photosensitivity-inducing drugs [86, 87], leading to both phototoxic and photoallergic reactions [87] (level of evidence 3). The potency to elicit photosensitivity varies among the different quinolones, being suggested that pefloxacin and fleroxacin are the most potent inducers of photoallergy, while enoxacin, norfloxacin, and ofloxacin are less able to induce this type of reactions [88] (level of evidence 3).

Vasculitis syndromes related to different quinolones have occurred [89, 90], being the majority of them induced by ciprofloxacin [89, 90] (level of evidence 3). Other skin reactions like bullous pemphigoid triggered by ciprofloxacin [91] and levofloxacin [92] have been described (level of evidence 3).

Hypersensitivity pneumonitis [93, 94], interstitial nephritis [95, 96], and hepatitis [97-99] associated with quinolone therapy have been also described (level of evidence 3). A publication of the Drug-Induced Liver Injury Network described 12 cases of fluoroquinolone-induced liver injury, most of them induced by ciprofloxacin [97] (level of evidence 3).

Diagnosis

Diagnostic procedure in HSRs to quinolones should include clinical history, STs, *in vitro* testing, and DPT [14, 100, 101]. The diagnosis is complex due to several factors: heterogeneous clinical picture, insufficient understanding of the pathogenesis of the HSRs, and finally the limitations and lack of standardization of the available *in vivo* and *in vitro* diagnostic tests [57].

The diagnostic procedure can be divided into two parts, which differs between the acute stage and remission:

1.- During the acute phase, the main question is whether or not the symptomatology is caused by a HSR. It is crucial a detailed history of previous exposure and tolerance to the culprit drug and a detailed description of the clinical picture. For IRs, it is important the assessment of cells involved and mediators released during the reaction, such as tryptase [42, 102, 103]. The determination of peak serum tryptase level 30-120 minutes after the onset of symptoms with subsequent comparison of the quantification of baseline levels [42, 103-105]. It has been suggested that the ≥20% above baseline level plus 2 µg/l is the minimal clinically significant elevation [106] (level of evidence 2+ grade of recommendation C).

For NIRs, the determination of enzymes levels indicating liver or kidney involvement and the presence of eosinophilia are sometimes enough indicators of drug HSRs [107]. Skin biopsy and viral serology may be also useful for confirming the diagnosis and discarding other possible causes [103, 108, 109] (level of evidence 3 grade of recommendation D).

2.- After remission of the acute reaction, patients may require further allergological evaluation in order to find out which of the different drugs taken may have caused the reaction. This can be done by certain *in vitro* tests, STs, or DPT.

Clinical history

A detailed clinical history is crucial to determine if a certain symptomatology reflects drug HSRs, as well as to clarify which is the eliciting drug. However, the appearance of similar symptoms do not allow distinguishing the underlying mechanism, which may be due to quite different immune and even non-immune mechanisms) [110, 111]. Data that have to be recorded are [101]: demographic data (such as age, sex, occupation, race), personal and

familiar history focused on drug allergy and other pathologies, a detailed description of the symptomatology, the time interval between the last drug administration and the onset of the reaction, cofactors (such as fever, viral infection, photosensitivity, stress, exercise), quinolone involved in the reaction as well as other drugs taken at the moment of the reaction and the reason for quinolone intake, the dose and the route of administration, previous tolerance to these drugs, time elapsed between the beginning of the reaction and the resolution, and the treatment administered for the resolution of the reaction (level of evidence 4, grade of recommendation D).

Skin tests

The diagnosis of HSRs to quinolones by STs is controversial, according to clinical experience and previous studies.

For IRs, the procedure generally begins with SPT, and if negative, IDTs [100]. The usual doses for SPTs and IDTs dilutions shown in Table 2 (level of evidence 2-, grade of recommendation C). However, from the first publications on this matter, the usefulness of STs has been controversial [112], as most studies show that quinolones can induce false-positive results due to the capacity of some quinolones to directly induce histamine release because of mast cell activation [9, 68]. Depending on the authors, ST results are assessed as non-specific [9, 38-40, 68, 113], or confirmed as allergic [114-120] (level of evidence 2-), being DPT the only diagnostic method to identify the culprit drug or an alternative quinolone [37, 46]. It has been suggested that the presence of a positive ST to any of the components of the group would suggests a mast cell activation (either by IgE dependent mechanism or by MRGPRX2 pathway), and this needs confirmation by DPT, although a positive DPT cannot discriminate between both mast cell activation mechanisms [121] (level of evidence 4).

- The sensitivity of STs is estimated to range from 41% to 80%, with specificity ranging from 46.5% for all STs to 29% for IDTs [12, 37, 70, 122, 123] (level of evidence 2-). The positive predictive value has been reported to range from 14.8% for all STs to 12% for IDTs [45, 123, 125] and the negative predictive value of 94-95.2% for all STs and 90% for IDTs [45, 123], similarly to other publications [37, 70, 122, 123] (level of evidence 2-). Due to the facts that most of studies include a low number of patients, that quinolones produce a large number of false-positive results attributed to non-specific histamine release, mainly by IDTs [38, 40], and that the negative value of STs is important when deciding to perform DPTs (grade of recommendation C), we

recommend including only SPTs and not IDTs in the diagnostic approach for IRs to quinolones, as negative results are useful to evaluate the introduction of alternative quinolones (level of evidence 4, grade of recommendation D).

For NIRs, the evaluation includes delayed-reading IDTs and patch tests (PTs) [100]. Positive PT results have been reported [125, 126] (level of evidence 3, grade of recommendation D). When photosensitivity reactions are suspected, photo-PTs with ultraviolet A light exposure can be performed [127]. However, photo-PTs are usually negative in most publications [128, 129] (level of evidence 3). This could be due to false negative results caused either by the inadequate concentration of the drug used, by the type of vehicle, or by poor skin absorption. The introduction of technical variations, such as pre-scarification in the photo patch area, could increase sensitivity [130] (level of evidence 3, grade of recommendation D). Cross-reactivity between lomefloxacin, ciprofloxacin, and fleroxacin has been observed in previous studies with positive test results [131] (level of evidence 3).

In FDE, the results of PTs in the affected area are usually negative. Positive PTs to ofloxacin and ciprofloxacin have been reported with 20% vaseline concentrations in a case reporting a reaction to ofloxacin [132]; positive PT to levofloxacin in the affected area, and cross-reactivity with ofloxacin in a case reporting a reaction to levofloxacin [133]; and in a case with positive PTs to ofloxacin 2% in dimethylsulphoxide in healthy skin [134] (level of evidence 3). In some Spanish studies, in which the preparation dimethylsulfoxide has been used as a vehicle and with quinolones at a concentration of 10%, negative results have been obtained [51, 135], being more usual the use of preparations with vaseline, also at 10% of the drug, although variable concentrations between 5-20% have been used with similar negative results [50, 72, 73, 136, 137] (level of evidence 3, grade of recommendation D).

In the rest of the skin, processes referring to vasculitis, purple, exudative erythema, or TEN hamper the possibility of performing *in vivo* tests due to the high risk of inducing the original reaction or even a worse one after the new contact with the drug. Therefore, in SJS and TEN, PT can be considered if there is a benefit of diagnostic information obtained, whereas delayed reading IDT is contraindicated [138] (level of evidence 4, grade of recommendation D).

***In vitro* tests**

Most *in vitro* tests for identification of the responsible quinolone are produced in-house due to the lack of current validated commercial ones.

For IRs, *in vitro* tests can involve basophil activation test (BAT) and immunoassays for detecting quinolone-sIgE. They are potentially useful for the diagnosis [139] (grade of recommendation C), and also for deciding whether to carry out DPT or not.

Determination of sIgE to quinolones has been reported by radioimmunoassay (RIA) using quinolone coupled to an epoxy-activated Sepharose 6B as the solid phase, with high specificity confirmed with an inhibition assay and a lower sensitivity (30-55%) [9, 25] (level of evidence 2-). The involved quinolone, the severity of the reaction, and the time interval between the reaction and the study can be the cause for the differences in sensitivity found in both published studies. Therefore, better results have been found when ciprofloxacin is the culprit, in less severe reactions and when the test was performed close to the reaction [9, 25], as a loss of sensitivity over time has been reported for IgE-mediated HSRs to others drugs such as betalactams [140], dypirone [141], and NMBAs [142] (level of evidence 2-).

BAT has been also found to be useful for *in vitro* evaluation of IRs to quinolones although with very different results regarding sensitivity and reliability [9, 12, 43, 47] (level of evidence 2-). Reported sensitivity ranges widely (from 0% [47, 68] to 90% [12]) as well as specificity (from 80% [9] to 100% [47]). It is of note that not all IRs induced by quinolones are IgE-dependent but also resulting from alternative IgE-independent effector cell activation such as through off-target occupation of the MRGPRX2 receptor [34, 35]. Because basophils barely express MRGPRX2, these cells will not respond in steady-state conditions of classical BAT [33]. Therefore, it is not known if a negative BAT reflects insufficient sensitivity of the method, or if a reaction is mediated by MRGPRX2 and is undetectable by means of measurement of CD63/CD203c expression [35].

As mentioned above with RIA, BAT sensitivity is also related to the culprit quinolone, the severity of the reaction, and the time interval between reaction and performance of the test, as well as to the use of additional quinolones [12, 43] (level of evidence 2-, grade of recommendation C). Indeed, when moxifloxacin is involved, BAT sensitivity was 41.7% when only moxifloxacin was used, increasing sensitivity up to 79.2% when both moxifloxacin and ciprofloxacin were included in the tests [9]. However, when ciprofloxacin was the culprit, the inclusion of moxifloxacin in the test did not improve the sensitivity. These findings may be due to the chemical structure and photodegradation of the molecules. Moxifloxacin has been shown to have a higher rate of photodegradation than ciprofloxacin [44], reducing the positivity of the test from 35.7% to 17.9% when BAT was not carried out in dark conditions [44]. Moreover, the activation marker used in the test can also affect the sensitivity, as ciprofloxacin preferentially upregulates CD63, whereas moxifloxacin induces greater

upregulation of CD203c [43]. This could be related to the severity of reactions, as moxifloxacin induces anaphylaxis more frequently than other quinolones [10, 12, 24, 43, 58], and it has been reported an upregulation of CD203c in patients who suffered anaphylactic shock, and a CD63 upregulation in patients with anaphylaxis and urticaria [43, 143-145]. It has been confirmed that BAT response to quinolones is mainly IgE-mediated as it was inhibited by the phosphatidylinositol 3-kinase (PI3K) inhibitor wortmannin [9]. PI3-K has been shown to be one of the important kinases activated by FceRI receptor cross-linking involved in IgE-mediated stimulation of human basophils [146], therefore if basophil activation is inhibited by wortmannin, the activation of basophils is IgE-mediated [9]. However, some reports indicate that the enzyme PI3K could be also involved in the activation by MRGPRX2 [147]. Thus, results of wortmaninn inhibition assays must be interpreted with caution. Nevertheless, the barely expression of MRGPRX2 in basophils could hamper its activation by this pathway.

For NIRs, most studies use the lymphocyte transformation test (LTT) for confirming T-cell involvement in NIR pathogenesis such as MPE and AGEP [69, 86, 148] (level of evidence 3, grade of recommendation D). LTT has shown a higher sensitivity than PTs, which can be due to the complex inflammatory response in the skin, a low capacity of quinolone to penetrate the skin or to the use of low quinolone concentrations in PT [69, 149] (level of evidence 3).

In recent years, other in vitro tests have been used such as ELISpot, that measures the number of cells producing IFN-g or IL-4. However, to our knowledge only one patient reporting ciprofloxacin induced exanthema has been reported giving negative result [150] (level of evidence 3, grade of recommendation D).

Further proof of the involvement of T-cells in NIRs can be obtained by assessing if peripheral blood mononuclear cells photo-modified with quinolones using ultraviolet A light are able to stimulate homologous cell proliferation, as demonstrated in photoallergy studies [148, 151] (level of evidence 3, grade of recommendation D).

Drug provocation test

DPT is defined as the controlled administration of a drug in order to diagnose HSRs [14]. It is considered the gold standard to establish or exclude the diagnosis of HSRs to quinolones when no other test is available [2, 14] (level of evidence 4, grade of recommendation D). It is also useful to choose alternative quinolones and to evaluate cross-reactivity [2, 14, 15, 70] (level of evidence 2+, grade of recommendation C).

DPT is not a risk-free procedure and must be performed under medical surveillance by trained personnel in a clinical setting where adequate treatment can be administered if a reaction

occurs [14]. DPT after negative *in vitro* and STs should only be considered after balancing the risks and benefits for the individual patient [14, 153] (level of evidence 4, grade of recommendation D). Different authors [14, 152, 153, 154] agree that in anaphylaxis or in severe reactions, DPT with the culprit or structurally/pharmacologically related quinolones is not indicated (level of evidence 4, grade of recommendation D). Therefore, taking into account the high incidence of severe HSR induced by quinolones, the role of DPT in confirming/excluding the diagnosis of HSR to quinolones is limited. In most studies using quinolones, DPT is performed in a single-blind placebo-controlled manner. Doses and number of steps used in DPT vary depending on the study, usually all of them escalating doses until the full therapeutic dose is achieved in one or two days [12, 15, 37, 46, 155]. Nevertheless, there are procedures with only two doses, 1/10 and 9/10 of the full therapeutic doses in non-anaphylactic reactions [152], and in NIRs full therapeutic doses are used several days afterwards [152] (level of evidence 2+, grade of recommendation C) (Table 3). There are controversies about the length of DPT protocols for NIRs as it has been reported with betalactams. In this sense, prolonged DPT at home have reported to provide higher negative predictive values than shorter ones [156-160] although with more side effects and health and cost impact related to disturbances of the intestinal microbiota in children [161] and risk of microbial resistance [162].

The procedure must be stopped when cutaneous and/or respiratory symptoms or changes in vital signs appear after a test dose, and, after evaluation, symptoms must be treated [2]. However, we have to take into account that concerning NIRs, symptoms may appear 24 hours or more after the initial dose [68, 152]. Photographs or detailed descriptions are essential in these cases [152] for further evaluation by the allergist (level of evidence 4, grade of recommendation D).

The rate of positive results in DPT in IRs depends on if other tests have been previously carried out [163]. Therefore, DPT was positive in 32.8% of cases previously studied with negative BAT [15]; in 35.3% of cases previously studied with negative sIgE [25]; in 12% of patients previously studied with negative STs [68]; and in 27.3% of cases not previously studied with other tests [163].

Regarding DPT with alternative quinolones, up to 50% of cases show cross-reactivity [36], being levofloxacin the safest quinolone [46] (level of evidence 2+, grade of recommendation C), although available data in literature are limited [152].

In many of the local reactions that occurred after intravenous administration, the drug was later tolerated [12], suggesting a toxic/irritative mechanism or the implication of a mechanism

through mast cell degranulation, via occupation of MRGPRX2 as it may occur in other non-IgE mediated reactions [33].

There is evidence that some patients with IgE-mediated reactions could lose sensitivity if no re-exposure occurs [140-142] (level of evidence 2+, grade of recommendation C). Therefore, the time interval between the suspected HSR and the DPT can affect the outcome of the test. Based on a small number of studies [68, 70, 163] of patients with IRs to quinolones who underwent DPT with the culprit drug, most patients tolerated the drug upon re-exposure (level of evidence 2-, grade of recommendation C).

Cross-reactivity

Cross reactivity among quinolones is nowadays controversial and represents a problem that has not been resolved yet [57]. Some studies focused on case reports or series with very few different quinolones involved suggest that this cross-reactivity is high, up to the 50% [12, 37], while in others studies, focused on larger series, the degree of reactivity is lower [46, 117] (level of evidence 3).

Cross reactivity among different quinolones seems to be related to the molecular ring common to all of them that may perform as the antigenic determinant [164]. In addition, changes in position C-1, C-5, C-7, and C-8 that differ between different quinolones may also affect the cross-reactivity among them [46].

There are no general rules to predict cross-reactivity among different quinolones and different patterns of cross-reactivity have been reported for IRs and NIRs. Different degree of cross-reactivity between quinolones from different generations has been reported in IRs. It has been published a high degree of cross-reactivity between quinolones of first (nalidixic acid) and second generation (norfloxacin, ciprofloxacin) [112], and a low one with quinolones from the third generation such as levofloxacin [46, 165] and other newer quinolones such as moxifloxacin [121, 166] (level of evidence 3). This could be explained by the different metabolites generated. Levofloxacin is the levogyre form of ofloxacin that results in specific cross-reactivity pattern [46] (level of evidence 3). *In vitro* studies for IRs suggest also a high degree of cross-reactivity between fluoroquinolones [9, 25] (level of evidence 3).

SIgE towards more than one quinolone was found in 63.6%-80% of cases when using RIA, and 48.2% of cases when using BAT. Although high, it must be taken into account that cross-reactivity demonstrated by *in vitro* test can be overestimated as only 16% of these patients reported a reaction to several quinolones [9, 25].

Different grades of cross-reactivity can also occur among quinolones of different generation in NIRs. Quinolones can interact with a great variety of human TCR. Some of them are highly specific for one compound while others show high cross-reactivity, which might be the basis for the cross-reactivity observed [167] (level of evidence 3). It has been published the possibility of three different reactivity patterns through three different T-cell clones: clones exclusively reacting with the eliciting drug, clones with a limited cross-reactivity, and clones showing a broad cross-reactivity [167]. In the case of photoallergic reactions, cross-reactivity among different quinolones has been demonstrated using a murine model, suggesting the existence of a common epitope recognized by quinolone-specific T-cells [168].

HSRs to quinolones have also been associated with allergic reactions to NMBA, as IgE against quaternary ammonium has been determined in 53% of patients with IRs to quinolones [27], although the *in vivo* relevance of these findings remains unclear (level of evidence 3). Nevertheless, more studies are needed concerning cross-reactivity with these drugs as well as with others.

Management

The management of HSR to quinolones is based on discontinuation of the offending agent, initiation of alternative agent, and supportive care (adrenaline, corticosteroid, antihistamines, fluid replacement or short acting beta-adrenergic agonist can be used based on the clinical severity of the manifestation) [57, 169].

When HSRs to quinolones are diagnosed, patients must avoid this group of antibiotics, being important to offer alternative drugs (grade of recommendation D). When therapeutic alternatives do not exist, it is important to assess cross-reactivity to other quinolones (grade of recommendation D), especially in patients with a previous history of HSRs to other antibiotics, for whom the therapeutic alternatives are decreased. When a specific quinolone is the only therapeutic option available, desensitization may be indicated (grade of recommendation D). It is not possible to establish a standard protocol as only few reports have been published. Three of them reported IRs induced by ciprofloxacin confirmed by DPT or ST. The route of administration of the drug was oral [170, 171] and intravenous [172], achieving the full therapeutic dose in 4-6 hours. In others publications, two cases of NIRs induced by ciprofloxacin were reported, reaching the full dose in 6 days [173] and a patient reporting FDE induced by ciprofloxacin in which a protocol of 10 days for achieving the total dose previously used for cotrimoxazol was carried out [174]. There is another case described in the literature, a patient allergic to levofloxacin in which a 24-hour protocol desensitization by continuous

intravenous infusion was performed [175]. More recently, a rapid pattern of oral desensitization using moxifloxacin has been published [176]. Finally, the patient tolerated this drug for 4 months with pruritus in the thighs and trunk that was controlled with oral antihistamines.

Algorithm

The recommended diagnostic algorithm is provided in Figure 2. After a clinical history, suggestive HSRs can be classified into IRs or NIRs, if the time interval between the drug intake and the onset of the reaction is shorter or longer than 6 hours, respectively. If not suggestive of HRS, DPT with the culprit is recommended. If suggestive of HSR, the first approach is to perform *in vitro* tests (BAT for IRs, and LTT for NIRs) if available. Despite the high specificity of determination of sIgE to quinolones, we have not considered including it in the algorithm due to the low sensitivity detected in the scarce reported articles and because it is not routinely performed in daily clinical practice. For IRs, SPTs with the wider battery of available quinolones should be performed, with readings performed 15-20 minutes after application. For NIRs, delayed-reading IDTs and PTs should be carried out except for SJS and TEN, in which delayed reading IDT is contraindicated and PT can be considered if there is a benefit of diagnostic information obtained. If the time interval between the drug intake and the onset of the reaction is not recorded, the reported symptoms may provide clues about the type of the reactions: if the patient reports anaphylaxis/shock, the reaction may be considered IR, whereas if the reported reaction is MPE/FDE/DRESS/AGEDP, SJS/TEN the reaction may be considered NIR. The controversy appears when the patient reports urticaria. In these cases, we suggest to perform the recommended tests for both IRs and NIRs. In case of negative STs and *in vitro* test with the culprit quinolone, a DPT can be performed after a careful analysis of the potential risks and benefits. DPT is recommended with the culprit, except for severe and life-threatening reactions (anaphylaxis, shock, AGEP, DRESS, SJS, TEN). DPT with alternative quinolones is recommended in cases with a positive DPT with the culprit, if STs or *in* vitro test are positive with the culprit quinolone, and in severe or life-threatening reactions, always after performing a risk-benefit balance analysis.

When a HSR is confirmed and the culprit quinolone is the only therapeutic option available, desensitization may be considered.

Acknowledgments

We thank Professor María José Torres and Dra. Cristobalina Mayorga for their in-depth review of our manuscript.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Table 1. Clinical manifestations and tests used for confirmed the diagnosis of HSR to quinolones.

Type of reaction	Index reaction	Confirmatory testing and result	Evidence grade
IR	Urticaria/angioedema	BAT [12, 15, 46] SPT [12, 46, 68, 70] IDT [46, 68, 70] DPT [9, 12, 15, 46, 68, 70]'	2+
	Anaphylaxis	BAT [12, 15, 46, 68] SPT [12, 46, 68, 70] IDT [46, 68, 70] DPT [12, 15]	2+
	Kounis syndrome	BAT [67] Specific IgE [67]	3
NIR	Urticaria	Delayed-reading IDT [70] PT [12] DPT [12, 15, 70]	2+
	MPE	LTT[70] Delayed-reading IDT [70] PT [69] DPT [12, 15, 68, 69]	2+
	FDE	PT [12, 71, 72] DPT [12, 72, 73]	3
	AGEP	Histology [61, 75] PT [69] LTT [61]	3
	SJS/TEN	Histology [78, 79, 81]	3
	Vasculitis	Histology [89, 90]	3
	Bullous pemphigoid	Histology [91, 92]	3
	Hypersensitivity pneumonitis	Histology [93, 94]	3
	Interstitial nephritis	Histology [96]	3
	Hepatitis	Histology [97-99]	3

Abbreviations: BAT: Basophil activation test. DPT: Drug provocation test. IDT: Intradermal test. LTT: lymphocyte transformation test.PT: Patch test. SPT: Skin prick test.

Table 2. Drug concentrations recommended in STs.

Drug	SPT	IDT
Ciprofloxacin	2 mg/mL [68, 123]	0,02 mg/mL[123]
Levofloxacin	5 mg/mL [68, 123]	0,05 mg/mL [38, 123]
Moxifloxacin	1,6 mg/mL [40, 68]	
	Tablet 400 mg [123]	
	suspended in NaCl	
Norfloxacin	Tablet 400 mg [123]	
	suspended in NaCl	
Ofloxacin	2 mg/mL [68]	0,05 mg/mL [123]
	5 mg/mL [123]	
	Tablet 400 mg [121]	
	suspended in NaCl	

Abbreviations: IDT: Intradermal test. SPT: Skin prick test.

Table 3. Doses of quinolones used in DPT at intervals of 60 min [12, 15, 37, 46].

	Doses for IR (mg)	Doses for NIR (mg)	Follow up doses in IR and NIR (mg)*
Ciprofloxacin	5-50-100-150-200	1st day: 5, 20, 100. 2nd day: 125, 125, 250 mg	500
Levofloxacin	5-50-100-150-200	1st day: 5, 20, 100. 2nd day: 125-125-250	500
Moxifloxacin	5-50-100-100-150	1st day: 5, 30, 65 2nd day: 100-100-200	400
Ofloxacin	5-25-50-100-200	1st day: 5, 25, 50 2nd day: 100-100-200	400
Gemifloxacin	4-20-40-80-180	1st day: 4, 20, 40 2nd day: 80-80-160	320
Norfloxacin	5-50-100-100-150	1st day: 5, 30, 65 2nd day: 100-100-200	400

* At least 2 days of follow up.

Abbreviations: IR: Immediate reaction. NIR: Non-immediate reaction.

Figure 1. Chemical structures of quinolones according to the generation group.

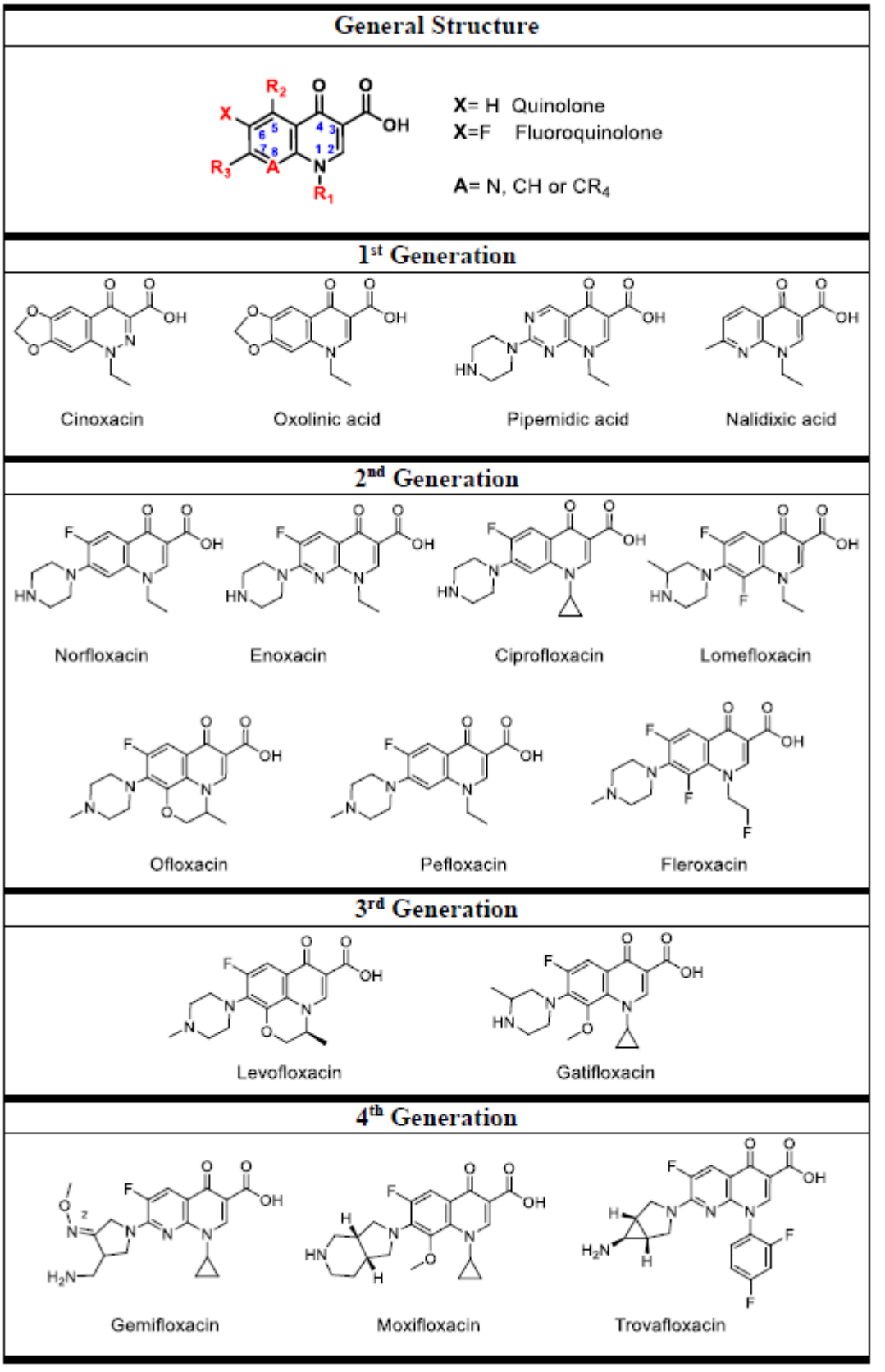
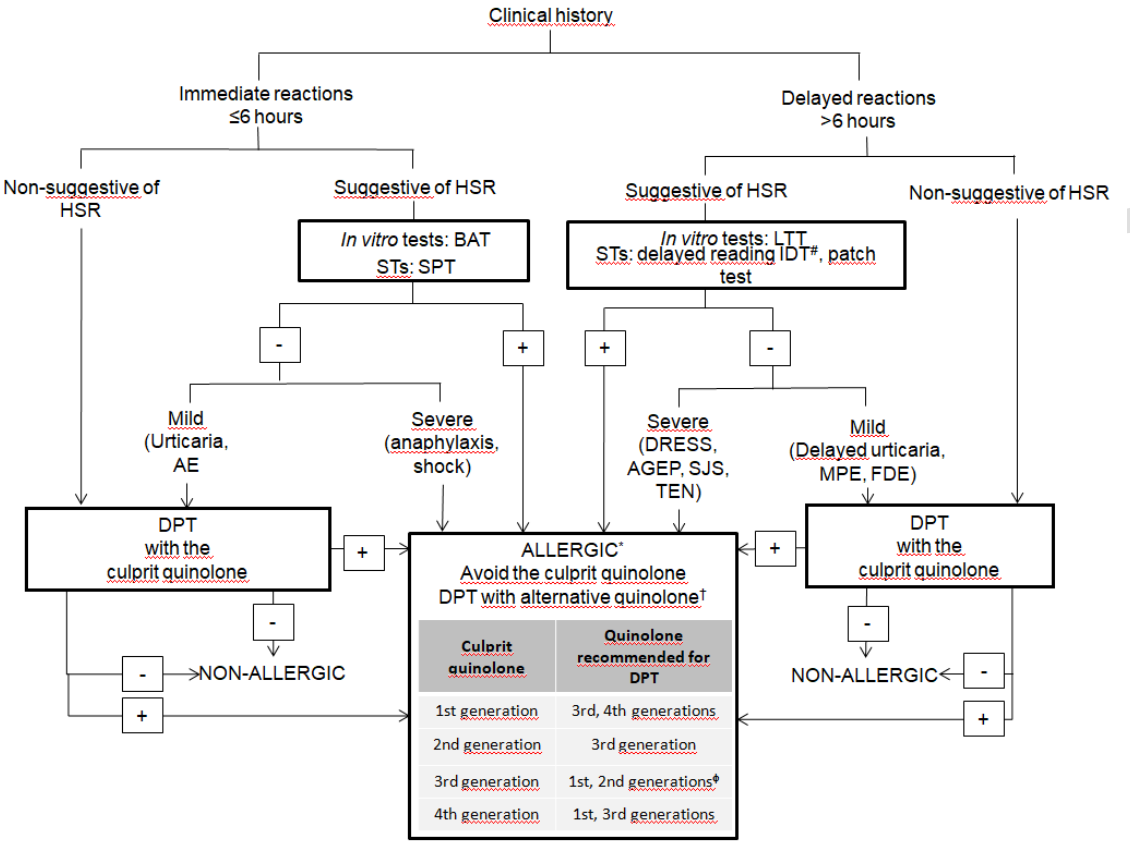


Figure 2. Diagnostic algorithm for diagnosis and management of HSRs to quinolones. Typically, IRs occur within the first hour following the first administration of a new course of treatment, although pathophysiologically it can be considered a time interval up to 6 hours after the quinolone administration.



Abbreviations: AE: Angioedema. AGEP: acute generalized exanthematous pustulosis. BAT: Basophil activation test. DPT: Drug provocation test. DRESS: Drug reaction with eosinophilia and systemic symptoms syndrome FDE: Fixed drug eruption. HSR: Hypersensitivity reaction. LTT: lymphocyte transformation test. MPE: Maculopapular exanthema. SJS: Stevens-Johnson syndrome. SPT: Skin prick test. TEN: Toxic epidermal necrolysis.

[#]Contraindicated in SJS/TEN

[*]If culprit quinolone is required, desensitization may be indicated.

[†]After a risk-benefit balance analysis.

[¢]Except ofloxacin due to potential cross-reactivity with levofloxacin

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